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Attorney Docket No.: 5739.200-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Weibel et al.

Application No.: 09/450,609 Group Art Unit: 1614

Filed: November 30, 1999 Examiner: J. Kim

For: NEW PHARMACEUTICAL COMPOSITION AND THE PROCESS FOR ITS PREPARATION

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Thyge Borup Hjorth declare that:

1. I am an inventor of the subject matter claimed in the above-referenced application. My Curriculum Vitae is attached hereto as Appendix A

2. I have reviewed the instant application, the Office Action dated July 3, 2001 and the cited prior art. In particular, I have reviewed the paragraph bridging pages 2 and 3 which states

> However, Applicants' attention is drawn to the example on page 35 of the Lohray reference (WO 97/41097) of record, where it teaches Applicant's composition comprising **lactose, magnesium stearate, cellulose** and corn starch, prepared with drying under reduced pressure. The difference between above reference and Applicant's claiming invention is the usual pharmaceutically acceptable excipients such as talc, lactose being employed is anhydrose and the specific cellulose. Applicants' are claiming a well known composition modified with usual, pharmaceutically acceptable excipients routinely

> incorporated in a tablet form in a low water content. The Lohray reference prepared the composition employing process of drying the mixtures under the reduced pressure. Therefore, Lorhray's[sic] composition obviates Applicants' composition of low water content, without showing result of improved stability alleged by the Applicants.....
>
> ...It is suggested that Applicants submit a declaration to clearly establish a surprising and unexpected result using Applicants teaching.

3. I have additionally reviewed section 2 of the instant Office Action entitled "Claims 6, 7, 9, 11-13, 16 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lohray et al. (WO9741097) in view of Sohda et al. (U.S. Patent No. 5972971)." Specifically, the Examiner states beginning in the paragraph bridging pages 5 and 6

> The difference between the primary reference and applicants' claimed invention is the presence of anti-oxidant set forth in claims 6, 14, and 15, and the proportions set forth in claims 8 an 9. However, to incorporate anti-oxidant to the primary reference would have been obvious to a person of ordinary skill in view of Sohda et al. who teach antidiabetic agent containing anti-oxidant and the other excipient. One in ordinary skill in the art would have been motivated to combine anti-oxidants to above composition since Lohray et al. teach other media normally employed can be incorporated and anti-oxidant is normally incorporated by Sohda et al. in formulating anti-diabetic agent....
>
> ...It is suggested, to advance the prosecution of the subject application, that a side by side comparison of stability be performed and results submitted per Rule 1.132 for review thy the Patent Office.

4. In response and in order to advance prosecution, the degradation of tablets containing high moisture content cellulose was compared with tablets containing low moisture content cellulose. The procedure followed is shown below.

5. Tablets were made by direct compression of powder mixtures containing the active compound and excipients. Different grades of micro crystalline cellulose were used to examine the influence on the chemical stability of the active compound. The tablets were put on stability and the stabilising effect was evaluated by analysing the content of degradation products by HPLC.

Compositions (1000 g batches):

Formulation A

Ingredient	Quantity
Active compound	0.914 g
Avicel PH 102	200 g
Mannitol	749.1 g
Magnesium stearate	5 g
Talc	45 g

A

Formulation B

Ingredient	Quantity
Active compound	0.914 g
Avicel PH 112	200 g
Mannitol	749.1 g
Magnesium stearate	5 g
Talc	45 g

B

Formulation C

Ingredient	Quantity
Active compound	0.914 g
Avicel PH 102	200 g
Anhydrous lactose	749.1 g
Magnesium stearate	5 g
Talc	45 g

C

Formulation D

Ingredient	Quantity
Active compound	0.914 g
Avicel PH 112	200 g
Anhydrous lactose	749.1 g
Magnesium stearate	5 g
Talc	45 g

D

Avicel PH 112 →

Avicel PH 102

All the ingredients were mixed and compressed into 300 mg tablets. The tablets were put on stability packed in high density polyethylene containers and stored at and 40°C/75% RH.

6. The data from the stability study is shown in the table below:

Formulation	Content (%) of degradation products after 6 months storage 40°C/75% RH
A	4.8
B	3.6
C	2.8
D	2.0

7. The data shows at 40°C/75% RH, that the formulations containing microcrystalline cellulose with low moisture content (Avicel PH 112, formulation B and D) are more stable i.e. lower content of degradation products than the formulations containing microcrystalline cellulose with higher moisture content (Avicel PH 102, formulation A and C). These results are certainly nonobvious and unexpected.

8. I declare further that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 21-Aug-2002

Thyge Borup Hjorth

Curriluculum Vitae
Thyge Borup Hjorth

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3520 Farum

Phone/E-Mail: 4495 2772 / 4443 4025 (work) / fogt-hjorth@mail.tele.dk

Personal information: 46 years old, married
Three children: 9, 13, and 16 years old

Education: Pharmacist in 1983, Ph.D. in 1987

Education and previous employment

Employment	**Responsibility, Experience**
1993→: Product Development, Novo Nordisk A/S	CMC Coordinator for NN622 since project start. Chairman for NN622 Supply group and NDA Stability group Formulation development of NN622 finished product. Gabitril Project: Responsible for development of extended release product via external companies. Responsible for stability systems in dept. 518 and representing Pharm.Dev. in Stability Focus Group
1989-1993: Benzon Pharma	Contract development of controlled release products for external companies Development of sterile products and solid oral dosage forms
1986-1989: H. Lundbeck A/S	Ph. D. project about stress conditions in powders during compression.
1983-1987: Royal Danish School of Pharmacy	Educated as pharmacist
1983	